Medical Officer's Review

NDA/BLA# 103000.5000
(ELN 1145)

Submission date: December 22, 2000
Review completed: November 9, 2001

Amendment A

Submission date: November 23, 2001
Review completed: March 4, 2002

Generic name or proper name: Botulinum Toxin Type A

Proposed trade name: BOTOX®

Chemical name: Botulinum Toxin Type A Purified Neurotoxin Complex

Product formulation(s) including adjuvants, preservatives, etc.: Sterile, vacuum-dried form of purified botulinum toxin type A, produced from a culture of the Hall strain of Clostridium botulinum, in a sodium phosphate/ammonium sulfate buffer with albumin human USP as an excipient without a preservative.

Sponsor: Allergan, Inc.

Pharmacologic Category: Neuromuscular blocker

Proposed Indication(s): Treatment of glabellar facial lines

Dosage Form(s) and Route(s) of Administration: To be reconstituted with 0.9% sterile non-preserved saline (2.5 mL will yield 4 U/0.1mL) and 0.1mL is injected intramuscular via a 30 gauge needle into each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 U.

Related Drugs: None

Related Reviews:
Chairperson/Product Reviewer: Julianne Clifford, Ph.D.
Statistical Reviewer: Boguang Zhen, Ph.D
Consultation: Ella L. Toombs, M.D., Medical Officer, CFSAN/OCAC
Consultation: Catherine A. Miller, CSO, OCBQ/APLB
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TABLE OF CONTENTS

OVERVIEW

On December 31, 1998, Allergan, Inc. submitted an IND with two separate but identical Phase III protocols to the Center for Biologics Evaluation and Research for its product BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex for the treatment of glabellar facial lines. A subsequent open-label safety study was also submitted with the intend to create a Supplemental Application to their Biologics Product Application for this indication and to have the label reflect this new indication.

BOTOX® is currently approved under Establishment License Number 1145 as of December 1989 for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and, as of December 2000, for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia. As this application is a clinical supplement for an approved product, the chemistry, manufacturing, and control information for both the active biological ingredient and the finished product as well as information on pre-clinical pharmacology, pharmacokinetics, and toxicology are incorporated via cross reference to the current ELN application for BOTOX® and appropriate INDs as agreed upon by the agency.

BB IND 723 Cervical dystonia

History of the sBLA

During initial pre-IND meetings, CBER Review Team members recognized that a significant amount of off-label clinical experience existed for the use of BOTOX® for treatment of hyperfunctional glabellar facial lines. The Review Team also recognized that answers to some of their concerns might be found within the published medical/scientific literature. Therefore, Allergan was advised to provide a comprehensive information package (complete study reports, rationale for dosing, rationale for efficacy endpoints, rationale for study design, clinical protocol and statistical analysis plan) that fully addressed concerns from information provided in the published literature and as components of a proposed, well-controlled clinical study protocol.

It was also determined that information obtained for rationale and validation of dosing and efficacy endpoints for the intended pivotal trials was obtained from clinical experience using BOTOX® manufactured from bulk toxin [redacted] However, approval for this new indication would be sought using BOTOX® from bulk toxin [redacted] The Review Team felt that historical data, although supportive for efficacy endpoint selection and general aspects of the study design, did not provide for an adequate safety database. More so, safety data derived from clinical studies of BOTOX® manufactured from batch [redacted] for the treatment of blepharospasm were also considered supportive but not as a replacement for actual, actively reported safety data for the treatment of hyperfunctional glabellar facial lines.

The new proposed indication has a cosmetic rather than a therapeutic benefit. Allergan's initial clinical development plan did not provide enough of a safety database to support a licensure application as provided in the 1994 ICH guidance document entitled, "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions". This document prescribes:

- (Item 4) A minimum of 300-600 patients treated for 6 months at dosage levels intended for clinical use.
- (Item 5) A cohort of 100 patients treated for a minimum of 1 year at dosage levels intended for clinical use.
- (Item 6) A total number of individuals treated with the investigational drug, including short-term exposure, of about 1500.

Therefore, the Review Team recommended that Allergan consider the above referenced guidance document. Sponsor agreed to conduct two identical, randomized, double-blind, placebo-controlled studies concurrently but independently. Each study would have at least 150 BOTOX® treated patients completing the study, providing a combined total of at least 300 BOTOX® treated patients to be followed for four months. Separate clinical study reports would be prepared for these two studies, but they would be combined for analysis in the integrated summaries of safety and efficacy (ISS & ISE) of the PLA Supplement for this indication. At the completion of the double-blind studies, all subjects from both studies would be recruited for enrollment into a single open-label study that would consist of two additional injections. Safety and efficacy evaluations of a minimum of 100 patients collected in the course of an open-label clinical trial over the course of a minimum of three treatments with this product for this indication would be submitted. Patients would be followed for four months after each injection to assess safety and efficacy. The study report for this clinical study would be included in the PLA Supplement for this indication. The PLA Supplement would contain the complete study reports for the double-blind stages and the open-label stages of these clinical trials.

The majority of the safety database would be collected in the course of the double-blind, randomized studies. In the review of the application, greater emphasis would be placed on data collected from the randomized, placebo-controlled, double-blind studies than on that from the open-label study. FDA encouraged Allergan to actively pursue the enrollment of non-Caucasian and male subjects to gather substantial safety and efficacy data in these populations. Allergan was asked to do subgroup analyses for safety and efficacy by race, gender, and previous BOTOX® treatment for facial lines, as well as ≥ 65 years of age to fulfill the geriatric labeling requirements. Allergan was also asked to perform an analysis of efficacy stratified by baseline severity at maximum frown.

Allergan was advised that a new CBER policy regarding the requirement for reproductive toxicity testing of products indicated for populations including women of childbearing age was being drafted. Allergan was reminded that their product/indication would be specifically marketed to members of that demographic group. It was recommended that Allergan design reproductive toxicology studies according to the guidelines provided in the ICH Guidance Document and submit those plans under the IND for review and comment to ensure that the preclinical studies were appropriately designed to provide the information needed for assessment of this product for this indication.
Allergan has submitted their comprehensive information package and has conducted the two identical Phase 3 efficacy studies and the Phase 3 open-label extended safety study.

Allergan submitted additional reproductive toxicity study reports on October 12, 2000 and has committed to conduct additional reproductive toxicity testing prior to the approval of this application.

Allergan is requesting a waiver from the requirement to conduct pediatric studies under 21 CFR 601.27 in the glabellar lines indication, as it is a condition of an aging population. No studies have been performed to date using BOTOX® in pediatric populations for this indication.

Discussion of Amendment A: On November 23, 2001, Allergan submitted an amendment to this supplement in response to the Agency's letter of November 15, 2001. In the letter, the Agency stated that the information and data submitted were inadequate for final approval action based on deficiencies in the label with regards to the sections entitled Clinical Studies, Indications and Usage, Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage, and Dosage and Administration. Specific comments and revisions to be made to the proposed labeling were included in the Agency letter.

Amendment A contains a revision of the original supplement submission to Section 8.9 "Integrated Summary of Safety Information" (ISS). In preparing their response to the Agency's requests, Allergan discovered that the incidence tables of the Adverse Events were inaccurate. These tables included events of placebo-treated patients from the two Phase III double-blind studies and excluded some BOTOX® treated patients from the open-label extension study from the analyses for the first treatment cycle of BOTOX®. None of the clinical study reports regarding effectiveness data were impacted.

The updated data has been incorporated into this review.

Material Reviewed (volumes which serve as a basis for this review):
Volumes 2-150.
Amendment A

Chemistry/Manufacturing Controls:

Product characteristics:
BOTOX® is a sterile, vacuum-dried form of purified botulinum toxin type A, produced from a culture of the Hall strain of *Clostridium botulinum*. The neurotoxin complex is a white-to-off-white suspension in a sodium phosphate/ammonium sulfate buffer. It is packaged in glass vials.

Each final BOTOX® vial contains:

- 100 mouse LD_{50} units of neurotoxin complex (active ingredient)
- 0.9 mg NaCl USP (excipient)
- 0.5 mg albumin human USP (excipient)

BOTOX ® is stored at ≤5°C. Upon use, BOTOX® is reconstituted with sterile, unpreserved, normal saline (0.9% sodium chloride injection, USP) and is be used within four hours after reconstitution, when stored under refrigeration.

One unit (U) of BOTOX® corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. The method utilized for performing the assay is specific to BOTOX®. Units of biological activity of BOTOX® cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. The specific activity of BOTOX® is approximately 20 units/nanogram of neurotoxin protein complex.

Animal Pharmacology/Toxicology:
There are known species differences in sensitivity to the various toxins. As little as 0.0003ug/kg of botulinum toxin type A can cause death in a mouse, and it has been estimated that as little as 0.1 ug ingested orally can be fatal for humans. Guinea pigs appear to be particularly sensitive. Rats appear to be less sensitive to Type B than to Type A.

Single dose toxicity studies have been conducted in rats, rabbits, and monkeys. All had BOTOX® administered IM, the intended clinical route. In chronic safety studies, BOTOX® was administered in repeat doses to rats and monkeys. The effects of BOTOX® on fertility and general reproductive performance were evaluated in rats. The embryo-fetal toxic and teratogenic effects of BOTOX® were evaluated in mice, rats, and rabbits. Testicular degeneration was observed in male rats receiving 24 U/kg. Doses of 8 and 16 U/kg were associated with a dosage-dependent reduction in male rat fertility. The reproductive NOEL for female rats was 8 U/kg. Provided impregnation occurred, there were no adverse effects on the numbers or viability of the embryos sired or conceived by treated male or female rats. Developmental toxicity was noted with doses of 8 U/kg. When instilled topically into the eyes, there was no ocular or corneal toxicity.

Botulinum toxin type A was first tested in monkeys more than 20 years ago to treat strabismus. The dose used was not systemically toxic and did not produce serious side effects. The LD_{50} for monkeys after intramuscular injection of botulinum toxin is approximately 40 units/kg. The toxic dose for humans is estimated to be similar.

Clinical Background/Rationale:
Clostridia botulinum is an anaerobic, gram-positive spore forming bacterium found throughout the world. It was first isolated and identified in the late 19th

century and shown to produce a potent protein neurotoxin thought to be the most lethal substance known on a per molecule basis. It initially received attention because of the toxic and lethal effects in humans associated with tainted food, infant ingestion of spores, and wound contamination. The toxin enters the vascular system and is transported to peripheral cholinergic nerve terminals. The central nervous system is not involved. Cranial nerve involvement almost always marks the onset of symptoms with subsequent symmetric descending paralysis that can lead to death. There is no sensory impairment. Typically there is no fever and patients are alert and orientated. In food-borne and wound illness, besides supportive care, equine antitoxin should be administered. There is no known mechanism to reverse the paralysis once it has occurred. Reversal occurs only gradually through what appears to be sprouting of new nerve terminals naturally. This may take several months and results in recovery of muscle function.

Botulinum Toxins
Different strains of C. botulinum have been identified to produce 8 different types of neurotoxin, designated types A, B, C_1, C_2, D, E, F, and G. Seven of these actually cause paralysis. Human botulism is largely limited to toxin types A, B, and E, or rarely type F. Types A and B toxins are resistant to digestion by GI enzymes. Type A disease is generally more severe than type B. Human illness from Type E is most often associated with improperly smoked fish. Type C and D botulism predominates in avian (predominately waterfowl) and nonhuman mammalian species. Type G has been associated with sudden death, but not with neuroparalytic ill.

All the toxins are zinc metalloproteases and their mechanism of toxicity is generally similar. All bind at specific receptor sites on cholinergic presynaptic terminals and block the release of acetylcholine. Toxin effects result in the failure of transmission at the neuromuscular junction. The mechanism of action is well understood and at least three steps are known to be involved in its inhibitory action. The toxin is heat labile.

As noted above, botulinum toxin type A is one of eight botulinum toxin serotypes produced by *Clostridia botulinum.* All clostridial neurotoxins are synthesized as a single inactive polypeptide chain (150 kD) and released (cleaved) by bacterial cell lysis. Cleavage or "nicking" by endogenous proteases activates the toxin and yields the active dichain form of the toxin: Light Chain (53 kD) and a Heavy Chain (97 kD) joined by a single disulfide bond and noncovalent bonds. Botulinum toxins are purified from bacterial filtrates in complex with other, non-toxic proteins. Botulinum toxin type A (BoNT A) exists in three forms: the M complex (300 kD) consisting of the neurotoxin plus a non-toxic non-hemagglutinin protein of similar size; the L complex (500 kD) and the LL complex (900 kD) which consist of a number of proteins with hemagglutinin activity in addition to the proteins in the M complex. Allergan describes BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex as a 900 kD complex

Botulinum toxins elicit flaccid paralysis by selectively blocking acetylcholine release at the neuromuscular junction. The Heavy Chain mediates a highly specific, high affinity binding of the toxin to peripheral nerves. The toxin is internalized by receptor mediated endocytosis followed by translocation across the vesicular membrane into the cytosol. Once in the cytosol, the Light Chain exhibits zinc-dependent endoprotease activity and selectively cleaves SNAP-25, a presynaptic membrane protein of the synaptic vesicle docking/fusion complex. Cleavage of SNAP-25 by BoNT A disrupts its function in the vesicle docking/fusion events and subsequently inhibits neurotransmitter release. Botulinum toxin does not affect the synthesis or storage of acetylcholine.

In the first two weeks after treatment with Botulinum toxin type A, the injected muscle begins to atrophy and the size of the individual muscle fibers change. This continues for approximately 4 weeks and then stabilizes. There is permanent inactivation of exposed cholinergic terminals. However, within 10 days of exposure, new unmyelinated axonal sprouts can be observed. New motor endplates are activated and muscle function is restored within approximately 3-6 months. Histologic changes may be observed as much as 3 years after Botulinum toxin type A injection, although the muscles are normal in terms of response and power.

In the 1960s, ophthalmologist Alan Scott, with the Smith-Kettlewell Eye Research Institute in San Francisco, began testing whether greatly diluted doses of the botulism toxin could relieve muscle spasms in the optic nerve. Clinical studies of botulinum type A for use in strabismus developed in the late 1970's. In 1989, the rights to this research were acquired by Allergan Inc. of Irvine (Orange County). That same year, Allergan won FDA approval to sell a drug called BOTOX® to treat certain eye spasms. By l992, the effect of BOTOX® on facial lines was reported in the literature (Carruthers and Carruthers, 1992; Borodic, 1992; Blitzer et al, 1993). The type A neurotoxin is presently the only type in widespread clinical use and commercially available. However, other serotypes are currently under investigation.

Relevant human experience:

Cosmetic use:

Glabellar facial lines arise from the activity of the underlying muscles of facial expression- the corrugator and orbicularis oculi muscles move the brow medially, and the procerus and depressor supercilii pull the brow inferiorly. This creates a frown or "furrowed brow". These muscles do not serve any other function. The location, size, and use of the muscles vary markedly among individuals. Lines induced by facial expression occur perpendicular to the direction of action of contracting facial muscles. An effective dose for facial lines is determined by gross observation of the patient's ability to activate the superficial muscles injected. A benefit of this mode of treatment is that it is temporary; therefore, if there is an adverse event, it will gradually diminish in time. Complications of other cosmetic procedures are generally more serious and long lasting.

Summary of Other Products Used:
Fillers (fat, silicone, gelatin matrix, bovine collagen) require anesthetic, do not address musculature, can have necrosis at the injection site, have reports of 50% volume loss after 1 year, have reports of vascular occlusion (fat) leading to blindness, allergic reactions (bovine collagen), and overcorrecting (fat).

Resurfacing techniques (phenol, TCA, dermabrasion, laser) tend to be more useful for the treatment of wrinkles than of lines, require anesthetic, do not address musculature, can have pigmentation changes, can have hypertrophic scarring (laser), can cause permanent photosensitivity (peels), have reports of liver, kidney and cardiac toxicity (phenol), and involve long healing periods.

Surgical correction that requires anesthetic can result in nerve injury (2.6%), alopecia (1%), hypertrophic scarring, requires concomitant fillers, can have hematoma (8.5%), which may lead to skin necrosis and involve a long healing period.

Important Information from related INDs and NDAs/BLAs
BOTOX® is currently approved under Establishment License Number as of December 1989 for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and, as of December 2000, for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia.

There is a tendency towards side effects due to temporary paralysis of other adjacent muscle groups. These side effects may be due to local spread of toxin from the injection site and/or misplaced injections. These effects generally resolve within two to four weeks. Results of clinical studies consistently report changes in clinical electromyographic parameters (i.e., jitter) in muscles distant to the site of BOTOX® injection. These data may indicate spread of the toxin via circulation, retro- or ortho-grade axonal transport, or some action of the toxin at a third, central, or unidentified site.

The most common side effect seen following the use of BOTOX ® for the treatment of blepharospasm is ptosis (reported to occur in approximately 16% of patients). Some patients have reported diplopia or symptoms resulting from the spread of effect to the mid-facial muscles. Long-term exposure has reportedly shown some fibrosis and atrophy of the orbicularis oculi muscles. Some patients have developed antibodies to botulinum toxin.

The most common side effect for the treatment of cervical dystonia is dysphagia and it appears to be dose-related. Occasionally subjects have needed nasogastric feeding tubes until improvement of swallowing and some have required IV therapy. This adverse event has consistently resolved over time. There have been rare reports of severe dysphagia in subjects with known as well as unrecognized neuromuscular disease.

There have been spontaneous reports of the apparent unmasking of a subclinical defect in neuromuscular transmission (myasthenia gravis) following the use of Botulinum Toxin Type A for the treatment of cervical dystonia.

In published literature of the use of BOTOX® in treating facial lines, there has been a single occurrence of diplopia, which resolved completely in three weeks. Transient ptosis, the most frequently reported complication, has been reported in approximately 5% of patients. A summary of published controlled studies shows:

Keen (1994)-	Ptosis 18% (2/11) Pain on injection 27% (3/11) Heavy feeling to forehead 9% (1/11) Change in eyebrow shape 9% (1/11)
Lowe (1996)-	Ptosis 20% (3/15)

A summary of a sample of published open-label studies shows:

Ahn (2000)-	Altered facial appearance 8% (3/38) Local swelling 5% (2/38) Ecchymosis 8% 93/38)
Blitzer (1993)-	Mild, temporary eyelid or lip weakness in "several patients". (Patients were treated for various facial lines).
Blitzer (1997)-	Ptosis 4% (7/162)

Carruthers (1992)-	Ptosis 11% (2/18) Headache 11% (2/18) Numbness 6% (1/18)
Carruthers (1994)-	Ptosis 10% Numbness 3% (1/31)
Ellis (1997)-	Ecchymosis 4% (1/23)
Foster (1996)-	Ptosis 18% (2/11) Headache 9% (1/11) Bruising at injection site 9% (1/11) Pain and burning during injection 100% (11/11)
Garcia (1996)-	Ptosis 5% 9/183 Ecchymosis at injection site 15% (28/183) Diplopia 1% (1/183)
Goodman (1998)-	Ptosis 17% (2/12) Bruising 42% (5/12) Headache 25% (3/12)
Guerrissi (1997)-	Ptosis 4% (2/54) Cutaneous rash and edema 4% (2/54) Ecchymosis 4% (2/54)
Guyuron (1994)-	Ptosis 11% (1/9) Minor local swelling 56% (5/9) Ecchymosis 33% (3/9) Burning sensation on injection 56% (5/9) General headache 44% (4/9) Mild nausea 11% (1/9)
Letessier (1999)-	Ptosis, asymmetric result, inadequate result, hematomas, headache (% given)

Carruthers has recommended steps to prevent ptosis:

1. The injected volume should be accurately dosed and kept to a minimum.
2. The toxin should be accurately placed and injected no closer than 1 cm above the central eyebrow
3. Injected areas should not be manipulated for several hours postinjection.
4. The subject should remain vertical for 2-3 hours postinjection.

The total number of subjects treated with BOTOX® in published reports is 961 subjects, 774 subjects in open-label trials.

Aminoglycoside antibiotics interfere with neuromuscular transmission and have been reported to potentiate the effects of botulinum toxin. Therefore, BOTOX® is contraindicated for patients taking aminoglycosides or other drugs that interfere with neuromuscular transmission.

There has been one study reporting the use of BOTOX® in pregnancy. Nine pregnant women received unreported doses of BOTOX®. One delivered prematurely, but was not thought to be related to the toxin.

The consequences of antibody formation have often been unclear in the medical literature. Antibody formation is the presumed mechanism of development of serum neutralizing activity. The factors that predispose patients to the development of antibodies are unknown, but some experience has shown that the risk is increased with the use of more than 300 U within a 30-day period. An exploratory analysis was conducted to examine the outcome of treatment in subjects treated for cervical dystonia. There did appear to be a difference in net treatment effect between the subjects without antibodies at baseline and those with antibodies at baseline when they were compared in a blinded, randomized manner, yet subjects did appear to subjectively experience responses when injected in open label treatment sessions. This analysis suggested that antibody formation is an important factor, and can lead to complete loss of response. Even after years of treatment with BOTOX®, patients can continue to develop antibodies. This may occur at a rate of 4% per two treatments (6 months). No serious adverse events associated with antibodies have been noted.

Off-Label Use:
The commercially available botulinum type A toxin has significant off label usage for the treatment of forehead wrinkles and furrows. Off-label use of BOTOX® by cosmetic surgeons accounted for 157,439 procedures in 1998. According to a study released by the American Society for Aesthetic Plastic Surgery, BOTOX® injections had the largest percentage increase of any cosmetic procedure performed in l998- up 142% from l997. This leads to confusion in terms of administration and the risk of adverse effects and lack of efficacy. Allergan would like to provide practitioners with guidelines for use and also to provide patients with information to more accurately assess the risks and benefits associated with choosing this method of treatment over other methods currently available.

Botulinum toxin type A is commercially available in the U.S. only from Allergan. In the United Kingdom and Europe, type A toxin (Dysport) is available as well as toxin manufactured by Allergan. (BOTOX®). The toxin manufactured by each company is from a different source of the organism. The clinical potency may be different. There is a large difference (factors 3 to 5) in the number of vial-labeled mouse- LD50 units used for comparable clinical effect. The two toxins are neither equivalent nor interchangeable on a unit for unit basis.

BOTOX® has been widely used in the U.S. off-label, as has Dysport in other countries, for a number of conditions, which involve involuntary muscle spasm, such as focal dystonias, cerebral palsy, hemifacial spasm, hand tremors, and headaches.

Foreign experience: Botulinum Toxin Type A Purified Neurotoxin Complex is currently approved for marketing in 69 countries, including the United States, under the trade names BOTOX®, BOTOX® 100 Units Allergan, BOTOX® 100U Injectable, Botulinum Toxin Type A Allergan, BOTOX® Lyophilisat, Allergan BOTOX®, BOTOX® 100 Units Per Vial or Clostridium Botulinum Toxin Type A.

Allergan had to temporarily suspend marketing in Portugal in September 2000 pending submission and receipt of standard documentation on human serum albumin from the supplier —— This information was submitted and accepted. Allergan resumed marketing BOTOX® in November 2000.

COUNTRY	INDICATIONS
Argentina	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. Hemifacial spasm, focal spasticity, including the treatment of upper limb spasticity associated with stroke in adults, cervical dystonia and the management of abnormal gait due to increased muscle tone associated with cerebral palsy patients, two years of age or older.
Australia	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. Treatment of dynamic equines foot deformity due to spasticity in juvenile cerebral palsy patients two years of age or older. Cervical dystonia.
Austria	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Bahrain	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.
Belgium	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Bolivia	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.
Brazil	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. Hemifacial spasm, muscular spasticity, **facial hyperkinetic lines** and hyperhidrosis.

Canada	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. To reduce the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults. Treatment of dynamic equines foot deformity due to spasticity in juvenile cerebral palsy patients.
Chile	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. Cerebral palsy, adult spasticity, tremor, dystonias, myoclonus, spastic disorders, back, neck and spinal pain related to contractures, bruxism.
China	Treatment of strabismus and blepharospasm
Columbia	Treatment of strabismus and blepharospasm. Hemifacial spasm and cervical dystonia. Cerebral palsy, spasticity, myoclonic disorders, migraine (tension-type headache), hyperhidrosis, back pain, neck pain and myofascial pain associated or due to an excess muscular contraction, chronic anal fissure, achalasia, essential tremor, spasmodic dysphonia and **facial hyperkinetic lines**.
Costa Rica	Treatment of strabismus, blepharospasm, hemifacial spasm and cervical dystonia.
Croatia	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. Reduction of signs and symptoms of cervical dystonia (spasmodic torticollis). Cerebral palsy.
Czech Republic	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. Reduction of signs and symptoms of cervical dystonia (spasmodic torticollis). Cerebral palsy. Focal spasticity
Denmark	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Ecuador	Treatment of strabismus and blepharospasm associated with dystonia. Hemifacial spasm. Cervical dystonia, spasmodic dysphonia, **hyperkinetic facial lines**, multiple sclerosis, chronic anal fissure, hyperactivity of the detrusor

	muscle due to spinal cord injury, myoclonic disorders and cerebral palsy related with spasticity.
Egypt	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.
El Salvador	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. Cerebral palsy, spasticity, myoclonic disorders, migraine (tension-type headache), hyperhidrosis, back pain, neck pain and myofascial pain associated or due to an excess muscular contraction, chronic anal fissure, achalasia, essential tremor, spasmodic dysphonia and **facial hyperkinetic lines**.
Estonia	Symptomatic relief of blepharospasm, hemifacial spasm and associated focal dystonias. Reduction of the signs and symptoms of cervical dystonia (spasmodic torticollis). Cerebral palsy.
Finland	Management of blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
France	Treatment of oculomotor disorders (strabismus, recent oculomotor paralysis and thyroid myopia), Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Germany	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Greece	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.

Guatemala	Treatment of blepharospasm and cervical dystonia. Achalasias, anal fissure, back pain, cerebral palsy, essential tremor, **facial hyperkinetic lines**, hyperhidrosis, migraine, spasmodic dysphonia, and spasticity.
Hong Kong	Treatment of strabismus and blepharospasm
Hungary	Blepharospasm, hemifacial spasm and associated focal dystonias. Reduction of the signs and symptoms of cervical dystonia (spasmodic torticollis). Cerebral palsy.
Iceland	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
India	Blepharospasm, hemifacial spasm and associated focal dystonias.
Indonesia	Treatment of strabismus and blepharospasm
Ireland	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Israel	Symptomatic relief of blepharospasm or VII nerve disorders in patients 12 years of age and above, hemifacial spasm and associated focal dystonias and strabismus. Reduction of the signs and symptoms of cervical dystonia (spasmodic torticollis). Treatment of dynamic equines foot deformity due to spasticity in juvenile cerebral palsy patients two years of age or older.
Italy	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Japan	Treatment of blepharospasm. Hemifacial spasm.
Jordan	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.
Korea	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or

	VII nerve disorders in patients 12 years of age and above. Treatment of cerebral palsy and cervical dystonia.
Kuwait	Blepharospasm, hemifacial spasm
Latvia	Blepharospasm, hemifacial spasm, associated focal dystonias, cervical dystonia
Lebanon	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.
Lithuania	Blepharospasm, hemifacial spasm and associated focal dystonias, cervical dystonia (spasmodic torticollis).
Luxembourg	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Malaysia	Treatment of strabismus and blepharospasm. Symptomatic relief of cervical dystonia in adult patients.
Mexico	Treatment of blepharospasm, strabismus, hemifacial spasm and focal dystonias. Cervical dystonia, cerebral palsy, hyperactivity of bladder detrusor, dysphonia, **facial hyperkinetic lines**, hyperhidrosis, migraine, pain associated with pathologic contractions of muscles in the back, bruxism, anal fissure and achalasia.
Netherlands	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. Cervical dystonia (spasmodic torticollis).
New Zealand	Treatment of strabismus, blepharospasm. Cervical dystonia.
Norway	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Oman	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.
Pakistan	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.
Panama	Treatment of strabismus and blepharospasm associated

	with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. Also hemifacial spasm.
Peru	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. Spasticity, dystonias, hemifacial spasm, focal dystonia, spasmodic dysphonia, contractions.
Philippines	Treatment of disorders of ocular muscle including strabismus and blepharospasm, neuromuscular conditions of the head and neck; cervical dystonia (spasmodic torticollis), hemifacial spasm. **Treatment of glabellar lines associated with corrugator and/or procerus muscle activity**.
Poland	Blepharospasm, hemifacial spasm and associated focal dystonias. Cervical dystonia (spasmodic torticollis). Cerebral palsy.
Portugal	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Russia	Treatment of strabismus, blepharospasm and hemifacial spasm. Treatment of dyskinesias (including cerebral palsy) in children.
Saudi Arabia	Treatment of strabismus, blepharospasm and hemifacial spasm and associated focal dystonia.
Singapore	Blepharospasm, strabismus, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Slovak Republic	Blepharospasm, hemifacial spasm, focal dystonias, cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in pediatric cerebral palsy patients, two years of age or older.
South Africa	Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. Dynamic equines foot deformity due to spasticity in pediatric cerebral palsy patients, two years of age or older.

Spain	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Srilanka	Treatment of strabismus and blepharospasm
Sweden	Blepharospasm, hemifacial spasm and associated focal dystonias. Idiopathic rotational cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Switzerland	Blepharospasm, hemifacial spasm, strabismus. Cervical dystonia (spasmodic torticollis). Cerebral palsy patients, two years of age or older. Focal spasticity, including spasticity of upper limbs associated with stroke.
Taiwan	Blepharospasm, hemifacial spasm and associated focal dystonias. Cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients.
Thailand	Treatment of strabismus and blepharospasm. Cervical dystonia (spasmodic torticollis). Cerebral palsy
United Arab Emirates	Treatment of strabismus and blepharospasm
United Kingdom	Blepharospasm, hemifacial spasm, cervical dystonia (spasmodic torticollis). Dynamic equines foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.
Uruguay	Treatment of strabismus and blepharospasm associated with dystonia.
Venezuela	Treatment of strabismus and blepharospasm associated with dystonia and hemifacial spasm.

Human Pharmacology, Pharmacokinetics, Pharmacodynamics

The chemical complexity of BOTOX® combined with its extreme potency limits the opportunity to study its pharmacokinetic profile in humans. Therefore, no human pharmacokinetic studies have been performed. BOTOX® is injected directly into the target organ, a skeletal muscle. Thus, bioavailability of the intravenous or oral route is not of clinical relevance.

The doses reported to be successful in eliminating glabellar lines vary among clinicians, although most practitioners recommend 20-30 units distributed over 1-3 injection sites per corrugator muscle and a single injection site in the procerus muscle. Dose ranging studies have shown that 1-3.5 units per corrugator were insufficient and concluded that 4 units per injection site in multiple injections sites were optimum for cosmetic paralysis of the corrugators (Rogers and Strinling, I998). These data support the doses chosen for the current trials.

Directions for Use:
BOTOX® is supplied as a single use vial, which contains 100 U of the neurotoxin. It needs to be reconstituted with 0.9% sterile normal saline that contains no preservative. Different amounts of saline instilled into the vial will result in varying doses of neurotoxin per o.1 mL. The diluent should be drawn up and slowly injected into the vial. The resultant product should be mixed gently to avoid bubbles. The solution is vulnerable to surface denaturation caused by bubbles associated with shaking. Therefore, care should be taken not to agitate the solution. The product should be administered within four hours after reconstitution.

Recommended dilution table:

Diluent Added (0.9% Sodium Chloride Injection)	**Resulting dose Units per 0.1 mL**
1.0 mL	10.0 U
2.0 mL	5.0 U
4.0 mL	2.5 U
8.0 mL	1.25 U

*Although not currently in the proposed label, the diluent needed to be added to achieve 4 U/0.1 mL is 2.5 mL to the vial.

The resulting solution (4 U/0.1 mL) is injected using a 30-gauge needle into each of five sites (o.1 mL per each site), two into each corrugator muscle and one into the procerus muscle for a total dose of 20 U.

In order to reduce the complication of ptosis, the health care provider should avoid injecting near the levator palpebrae superioris muscles. Injection of the medial corrugator muscle should be placed at least 1 cm above the supraorbital ridge.

Instructions given to investigators for use and administration during the trials were:

Corrugator muscle:

Beginning on one side, place the thumb or index finger firmly below the orbital rim in order to prevent extravasation below the orbital rim, and make one injection into the inferomedial aspect of the corrugator muscle near the origin of the supratrochlear nerve and another injection superolaterally into the superior middle aspect of the corrugator muscle at least 1 cm above the bony orbital rim. The needle should be orientated superiorly and medially during the injection. Repeat the procedure for the contralateral side.